REMARKS

Rejection Under 35 USC §112, 1st Paragraph

Claims 2-4 are rejected under 35 U.S.C. §112, first paragraph, for failing to comply with written description requirement. The rejection is moot as claims 2-4 are canceled.

Rejection Under 35 USC §101

Claims 1-8 are rejected under 35 U.S.C. §101 for lack of utility. This rejection is respectfully traversed.

The present invention describes a gene, *Evi27*, which is a member of the IL-17 receptor family. The Examiner acknowledges the identification of *Evi27* as a new member of the IL-17 receptor family. The Examiner, however, contends that the specification fails to provide a specific and substantial utility for Applicant's novel nucleic acid sequence. Applicant respectfully disagrees.

Substantial Utility

Applicant submits that there is substantial utility associated with the *Evi27* gene. First of all, the ligand for the *Evi27*-encoded cytokine receptor, IL-17E, which induces activation of NF-

kB and stimulates production of the proinflammatory chemokine IL-8, was identified at the time the invention was made (Lee et al. (2001), *J. Bio. Chem.*, 276:1660-1664). In addition, at the time the invention was made, it was reported that overexpression of IL-17E in transgenic mice resulted in a Th2-biased immune response and pathological changes characterized by mixed inflammatory cell infiltration, epithelial hyperplasia and hypertrophy in multiple tissues (Pan et al. (2001), *J. Immunol.* 167:6559-6567). These findings indicate that IL-17E is a unique pleiotropic cytokine and *Evi27*-encoded receptor is an important mediator of inflammatory and immune responses.

The present specification further teaches that the *Evi27*-encoded receptor plays important role in the homeostasis of tissue in health and disease beyond the immune system. The mouse orthology of *Evi27* was identified at a site common for retroviral integration in BXH2 murine leukemias (page 58, lines 2-5; page 59, lines 4-7). The human homologue of *Evi27* maps to chromosome 3p21, a region consistently deleted in a variety of human cancers (page 66, line 16 to page 67, line 13). Loss of 3p heterozygosity is frequently observed in renal cell carcinoma, lung cancer and breast

cancer, and 3p21 is a frequently deleted region in chronic myelogenous leukemia. It is generally known in the art that a number of cytokine and growth factor receptors have been implicated as oncogenes, reflecting the important roles these proteins play in control of cell growth. The present specification also teaches that *Evi27*-encoded receptor is a candidate for a new leukemia disease gene (page 58, lines 5-15). Taken together, these evidences indicate that the *Evi27*-encoded receptor would play important role in human diseases, particularly cancer and chronic inflammatory conditions.

Specific Utility

The present specification discloses a model for *Evi27*-encoded receptor in myeloid leukemia development (page 66, lines 3-15). Terminal differentiation of myelomonocytic precursor cells likely result in the down regulation of Evi27 expression. However, proviral insertions at Evi27 result in constitutive expression of the receptor. Binding of ligands to the Evi27 receptor would trigger the release of TNF-α and IL-1β by the leukemic cells. The secreted TNF-α and IL-1β would in turn provoke the production of multilinage hematopoietic growth factors, adhesion molecules, and

inflammatory cytokines by stromal cells. These stromal cell derived factors then support the growth and survival of the leukemia cell and may account for the absolute dependence of the B160 leukemia on the stromal feeder layer for growth and survival.

Thus, in view of the present disclosure that teaches *Evi27*-encoded receptor mediates secretion of proinflammatory cytokines and plays important role in the developmental and/or disease processes of myeloid leukemia cells, one of ordinary skill in the art would readily recognize a specific utility of the present invention in that modulating the expression of Evi27 at the RNA or protein level can be exploited to regulate the growth of myeloid leukemia cells. Applicant submits that one of ordinary skill in the art generally knows how to select and employ standard experimental methods to modulate gene expression at the RNA or protein level *in vitro* or *in vivo*.

Applicant further submits that once a gene such as the *Evi27* gene that possesses substantial biological properties as described above was cloned, one of ordinary skill in the art would readily recognize a specific utility in using the cloned gene to construct transgenic mice or knock-out mice. Transgenic or knock-

out mice are two powerful tools that were used by one of ordinary skill in the art at the time the invention was made to determine the biological functions of a particular gene. In view of the fact that *Evi27*-encoded receptor plays a substantial role in cancer and chronic inflammatory conditions, *Evi27*-transgenic or -knock-out mice could readily be constructed as animal model for the diseases.

In conclusion, Applicant submits that there is an asserted utility for the claimed *Evi27*-encoded receptor that would be considered specific, substantial, and credible by a person of ordinary skill in the art in view of all evidence of record. Accordingly, Applicant requests that the rejection of claims 1-8 under 35 U.S.C. §101 be withdrawn.

Rejection Under 35 USC §112, 1st Paragraph

Claims 1-8 are rejected under 35 U.S.C. §112, first paragraph, for lack of utility. This rejection is respectfully traversed.

A 35 U.S.C. 112, first paragraph, rejection should not be imposed or maintained unless an appropriate basis exists for imposing a rejection under 35 U.S.C. §101 (M.P.E.P. §2107.01 IV). As discussed above, Applicant submits that the specification has

provided specific and substantial utility for the *Evi27*-encoded receptor. In view of the present disclosure and the proposed model of myeloid leukemia development described herein, one of ordinary skill in the art would readily recognize that modulating the expression of *Evi27*-encoded receptor at the RNA or protein level can be exploited to regulate the growth of myeloid leukemia cells. Accordingly, Applicant respectfully requests that the rejection of claims 1-8 under 35 U.S.C. §112, first paragraph, be withdrawn.

This is intended to be a complete response to the Final Office Action mailed November 4, 2003. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

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